Remarks

Applicant has carefully considered this Application in connection with the Examiner's Action, and respectfully requests reconsideration of this Application in view of the foregoing amendment, and the following remarks.

Applicant has amended Claims 3, 4 and 5. Support for the amendments can be found in the specification as filed. No new matter has been added.
Accordingly, Claims 1 and 3-5 are presently pending in the Application.

I. Rejection under 35 U.S.C. § 112, First Paragraph

Claim 3 stands rejected under 35 U.S.C. § 112, First Paragraph for enablement. The Examiner asserts that the specification does not enable any person skilled in the art to which it pertains to make or use the invention. More specifically, the Examiner contends that while the specification supports enablement for synergistic effects as it pertains to inhibition of T-cell proliferation, it does not reasonably provide enablement for a claim that reads on any synergistic effect. The Examiner goes on to state that no facts or examples have been presented to show that the compounds act synergistically with respect to the disease. Applicant respectfully submits that newly amended Claim 3 is enabled under 35 U.S.C. §112, first paragraph, for the reasons discussed below.

Applicant need not have actually reduced the invention to practice prior to filing in order to satisfy the enablement requirement under 35 U.S.C. §112, first paragraph. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain a single example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d 904, 164 U.S.P.Q. 642 (CCPA 1970)), and "representative samples are not required by the statute and are not an end in themselves" (*In re Robins*, 429 F.2d 452, 456-57, 166 U.S.P.Q. 552, 555 (C.C.P.A. 1970)). Thus, 35 U.S.C. § 112, first paragraph, enablement does not require any working examples.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such

experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, enablement does not require a working example and experimentation is allowed so long as it is not undue.

Newly amended Claim 3 is enabled under 35 U.S.C. §112, first paragraph because the specification as filed amply supports claims reciting a method comprising administering to a patient in need thereof of a synergistically effective amount of a pharmaceutical composition comprising pimecrolimus in combination with calcipotriol or tacalcitol. The skilled artisan, armed with the disclosure provided in the application as filed, would have been able to determine, through routine experimentation, which amounts and combinations of the compositions provide a synergistic effect. Applicant directs the Examiner to paragraph 41 of the specification, and to Berenbaum and EPO427680 and EPO683156, which are cited therein at paragraph 42, for representative conventional methods for calculating and verifying synergetic effects of pharmaceutical compositions.

Moreover, Applicant directs the Examiner to paragraph 57 of the specification in which an example is provided for the use of pimecrolimus in combination with calcipotriol, including suitable unit dosages for oral administration.

Applicant submits that the kind of experimentation required for determining synergistic amounts of the compounds and their inhibitory effect on inflammation, while complex in some regards, is routine to one skilled in the art, and therefore, is not undue experimentation. Armed with the teachings of Applicant's invention and what was known in the art, the practioner would not need to engage in any undue experimentation to practice the invention commensurate with the scope of newly amended Claim 3, and Claim 3 is therefore enabled under 35 U.S.C. § 112.

As such, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of Claim 3 under 35 U.S.C. § 112, First Paragraph.

II. Rejection under 35 U.S.C. § 112, Second Paragraph

Claim 4 stands rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim subject matter. Claim 4

has been amended to read "calcipotriol or tacalcitol", support for which can be found at page 4 of the specification as filed. In light of the amended claim language, Applicant respectfully requests that the rejection of Claim 4 under 35 U.S.C. § 112 be reconsidered and withdrawn.

III. Rejection under 35 U.S.C. §§ 102/103(a)

Claims 1, 3-5 are rejected under 35 U.S.C. §§ 102 and 103(a) as being unpatentable over Van Etten et al. in view of WO 09/18468; Nghiem et al.; Paul et al.; Baumann et al. (U.S. Patent No. 5,912,238); Van De Kerkhof et al.; and Koo et al. (U.S. Pub. No. 2004/0202706). Applicant respectfully traverses the rejection.

The Examiner cites Van Etten for teaching a combination of rapamycin or tacrolimus (FK506) and the vitamin D analog $1,25(OH)_2D_3$. The Examiner also cites WO 98/18468 for the combination of rapamycin and $1,25(OH)_2D_3$ for the treatment of diseases of the immune system. A third reference, Nghiem is cited for teaching pimecrolimus and tacrolimus as structurally similar macrolide immunosuppressant. A fourth reference, Paul, is cited for teaching ascomycin derivatives as a novel class of anti-inflammatory macrolides. A fifth reference, Van de Kerkhof, is cited as teaching calcipotriol and tacalcitol as less hypercalcemic than the vitamin D analog $1,25(OH)_2D_3$. Bauman is cited by the Examiner for teaching pimecrolimus in the treatment of autoimmune and hyper-proliferative skin diseases.

Koo is cited by the Examiner; however, Koo was filed on January 8, 2004 and published on October 14, 2004 - after the priority date of Applicant's invention. Pursuant to 35 U.S.C. §§ 119 and 365, Applicant's claim the benefit of an earlier filing date; Applicant's Application No. 10/550,355 claims priority of PCT No. PCT/EP04/03512, which claims foreign application priority of GB 0307865.6, filed on April 4, 2003. Thus, Applicant is entitled to a priority date of April 4, 2003. As such, Koo is not available as a reference for the rejection under § 103(a).

Applicant respectfully asserts that the references cited by the Examiner, when combined, fail to teach the limitations of Claim 1 and newly amended Claim 3, which recites the use of a synergistic amount of pimecrolimus in combination with calcipotriol or tacalcitol for the treatment of dermatological diseases and inflammatory bowel

disease (IBD). As such, the references do not teach each and every element of Applicant's claimed invention.

Moreover, Applicant believes that the Examiner has incorrectly described the teachings of the references. In other words, Applicant respectfully asserts that the references do not say what the Examiner says that they do. Specifically, Van Etten presents as the goal of its study whether synergism could be observed with immunosuppressants other than rapamycin, namely mycophenolate mofetil, leflunomide and the methylxanthine A802715, or with analogs of $1,25(OH)_2D_3$. Variability in synergism for the different combinations were noted – synergism was not consistent - and was dependant on several factors, such as the kind of immunomodulator used, the kind of vitamin D analog used, dosages used, etc. Moreover, Van Etten does not teach nor mention pimecrolimus and even teaches away from the combination of immunosuppressants with vitamin D analogs because of the undesired calcemic effects seen with $1,25(OH)_2D_3$.

Nghiem is cited as teaching tacrolimus, however, this does not cure the defects of Van Etten because it does not suggest tacrolimus in combination with a vitamin D derivative. Nghiem is solely directed at a topical treatment for atopic dermatitis and there is no teaching or suggestion to applications beyond such treatment. It should also be noted that tacrolimus is not an ascomycin derivative, as is pimecrolimus, thus it would not motivate one skilled in the art to merely substitute pimecrolimus for tacrolimus as the Examiner seems to suggest.

While WO 09/18468 teaches the use of vitamin D derivatives, it is solely directed to rapamycin and calcitriol and does not teach calcipotriol or tacalcitol. Rapamycin is not a calcineurin inhibitor, as is pimecrolimus, thus there would be no basis for modifying the reference in a manner suggested by the Examiner.

Van de Kerkhof teaches tacalcitol ointment in the treatment of psoriasis. There is no discussion of combining tacalcitol with other compounds and treatment is solely directed to psoriasis. Nothing in Van de Kerkhof suggests applications to other diseases.

The Examiner cites Paul as teaching ascomycin derivatives as a novel class of anti-inflammatory macrolactams. Paul teaches tacrolimus for the treatment of psoriasis and discloses that "tacrolimus is not an ascomycin derivative". (See Paul, page 70.)

Thus, at the time of the invention, not only was there simply no disclosed use of pimecrolimus in combination with calcipotriol or tacalcitol for the treatment of dermatological diseases and IBD, there was no suggestion or motivation in the art to arrive at Applicant's invention. Applicant respectfully asserts that a person of ordinary skill in the art would not be motivated or suggested to combine the references as suggested by the Examiner.

For instance, a person of ordinary skill would know that while rapamycin and tacrolimus are related substances, they are isolated from different species of streptomyces and have different modes of action. For example, rapamycin is not a calcineurin inhibitor as is pimecrolimus, and tacrolimus is not an ascomycin derivative as is pimecrolimus. Thus, a person of skill in the art would not consider all macrolides as – per se – having the same functions and activities, in particular since this group is also a chemically diverse one. Furthermore, a synergistic effect of a combination of the macrolide with a vitamin D derivative cannot be expected for all combinations.

It is legally insufficient to conclude that a claim is obvious just because features of a claim can be independently shown in the art. The claimed combination of Applicant's invention is not suggested by the prior art and the art, when combined, is not a predictable use of prior art elements for their established functions. Applicant believes that such a conclusion could only be drawn through impermissible hindsight.

The Examiner states that calcipotriol and tacalcitol are disclosed to be effective in treating psoriasis; however, all teachings are for the vitamin D analogs alone – in topical ointments – to treat psoriasis. Nowhere is there a teaching or suggestion of oral dosage forms for the treatment of inflammatory bowel disease, nor a suggestion that their efficacy would be improved by co-administration with another therapeutic. Moreover, the teachings of the prior art show what a diverse group of compounds comprise macrolides and therefore, one skilled in the art would know that one cannot simply be substituted for another, as suggested by the Examiner.

No use of a synergistically effective amount of pimecrolimus in combination with a calcipotriol or tacalcitol for the treatment of dermatological diseases and IBD, as required by Applicant's Claim 3 is taught or suggested by the references cited by the Examiner. As such, Applicant respectfully requests that the rejection under 35 U.S.C. §§ 102/103 be reconsidered and withdrawn.

IV. Conclusion

In view of the foregoing, Claims 1 and 3-5 are in condition for allowance, and Applicant earnestly solicits a Notice of Allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this Application, the Examiner is invited to telephone the undersigned at the number provided.
Prompt and favorable consideration to this Amendment and Reply is respectfully requested.

Respectfully submitted,
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